REMARKS

At the outset, Applicants thank Examiner Michael Brannock, Supervisory Examiner Yvonne Eyler, Interference Specialist Anthony Caputa, and Director Jasemine Chambers for the courtesies extended during the interview ("the Interview") held on November 5, 2003 at the United States Patent and Trademark Office with Prof. James Broach of Princeton University, one of the inventors of the present application, and Laura A. Coruzzi and Eileen E. Falvey of Pennie & Edmonds LLP, the Applicants' representatives.

During the Interview, Applicants offered to cancel claims 43-58 and 60, without prejudice, to expedite prosecution, to narrow the issues and place the remaining Claim 59 in condition for allowance and obtain a declaration of an interference with U.S. Patent 5,691,188 by Pausch ("the Pausch '188 patent").

By this amendment, Applicants cancel Claims 43-58 and 60, without prejudice to Applicants' right to pursue the subject matter of the canceled claims in other applications. Claim 59 is the only claim pending in the instant application.

Claim 59 is directed to a transformed yeast cell useful in cell-based drug screening assays. In particular, the yeast cell of claim 59 is required to have a heterologous receptor, a hybrid Gα protein, and a reporter gene controlled by a pheromone responsive promoter. For the Examiner's convenience, Applicants attach a schematic that was referred to during the Interview to assist in explaining the patentability of the instantly claimed invention over the prior art of record. As depicted in the schematic (bottom center), the yeast cell of Claim 59 has a hybrid Gα protein comprised of a yeast portion (blue) and a mammalian or other exogenous portion (red). The hybrid Gα protein does two things: (1) it productively interacts with a heterologous receptor expressed by the yeast cell (upstream events, labeled "1") and (2) it also productively interacts with the yeast Gβγ subunit (downstream events, labeled "2"), thereby permitting signal transduction. Successful activation of the heterologous receptor by its ligand transduces a signal, mediated by the hybrid Gα protein, which results in expression of a reporter gene at the end of the pathway

(indicated by the light bulb).[1] Because a single hybrid Gα protein may be designed to adapt to different G-protein coupled receptors, the invention provides a versatile yeast cell which can be used as a universal screening system for receptor-ligand interactions.

The top of the schematic depicts the prior art systems of Sledziewski and King as well as the yeast cells of Kang. Sledziewski and King (top left and center, respectively), each teach alternative yeast cell-based assay systems that do not use hybrid Gα proteins. Briefly, the assay system of Sledziewki used a hybrid receptor that could interact with a mammalian ligand and yeast Gα protein. The system of King supplied the yeast cell with a mammalian receptor and its "matched" mammalian Gα protein that fortuitously functioned in yeast. Neither system is as versatile as the claimed invention -- for each target, Sledziewski requires engineering a chimeric receptor, and King hinges on the hope of identifying a "matched" mammalian receptor/ Gα protein pair that will function in a yeast host. Yet each is complete within itself for the intended purpose of yeast-based screening assays, as has been discussed previously. (For a more detailed discussion of these assay systems, the Examiner is referred to Applicants' Responses filed June 14, 2002 and April 2, 2003.)

The only reference that describes a hybrid Gα protein is Kang. However, the Kang yeast cell was not designed for drug screening. Kang's purpose was to dissect the functional domains of the yeast Gα protein. To this end, Kang constructed hybrid Gα proteins (represented in Kang, Figure 2), and tested them for productive interactions with yeast signaling pathway components. Kang tested the ability of the hybrid Gα proteins to substitute for native yeast Gα in the downstream pathway. As shown in Kang Table 2, some of Kang's hybrid Gα proteins were able to complement the Gα mutant, indicating an interaction between the hybrid Gα and Gβγ subunits (*i.e.*, the downstream components of the pathway shown as "2" in the attached schematic), but not with the yeast receptors (*i.e.*, the upstream components of the pathway shown as "1" in the attached schematic; *see* Kang, Abstract, Fig. 5C, and page 2588, col. 2, first full paragraph).

Based on the knowledge gained by dissecting the domains of the yeast Gα hybrids, Kang speculated that it might be possible to design a hybrid Gα construct that would

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[1] The yeast cells also lack the native Gα subunit due to an SCG1/GPA1 mutation (not depicted in the schematic), so that signaling through the native Gα subunit will not interfere with the assay.

interact with both the yeast receptor and the downstream components of the signaling pathway. However, when they tested this hybrid Gα protein, it failed. As reported on page 2588, col. 2, last complete paragraph:

> Because our results suggest that Gαs can bind to yeast βγ, we speculated that the αs-Scg1 hybrid (Fig.2) might be able to interact with both βγ and the pheromone receptors and thus allow pheromone response and mating. Instead, expression of this hybrid protein at a level similar to the levels of the functional constructs *failed to produce a detectable phenotype*. No definitive conclusion can be made from these negative results, although the lack of function of this hybrid protein suggests that its structure may be abnormal. (*Emphasis added.*)

Thus, Kang did not succeed in designing a hybrid Gα protein which could productively interact with both the yeast receptor and the downstream signaling pathway. In view of Kang's failure, the skilled artisan would not have been motivated to use Kang's hybrid Gα protein in combination with the chimeric receptor of Sledziewski or the mammalian receptor of King.[2]

In contrast, the Applicants have taught "the rules" for constructing hybrid Gα proteins so that they interact *both* with a heterologous receptor *and* with the downstream components of the yeast signaling pathway. Indeed, a detailed roadmap for constructing such hybrid Gα proteins is provided by the instant application and the earliest filed priority

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[2] During the interview, the Examiner cited to a 1999 publication by Pausch as ostensible support for a motivation to use the chimeric Gα proteins of Kang for coupling mammalian receptors to yeast signal transduction systems. (Pausch *et al.*, Ch. 11, *in* "Identification and Expression of G Protein-Coupled Receptors," Kevin R. Lynch ed., 1999, pp. 197-212 at 206). The Applicants disagree with the Examiner's assessment of Pausch 1999. Nevertheless, Pausch's interpretation in 1999 does not change what Kang had to say about his own work in 1990, and certainly does not reflect what the "take-home" lesson would have been to one of ordinary skill at the relevant time period in 1993. By relying on this 1999 publication, the Examiner has, perhaps, unwittingly fallen prey to the vagaries of hindsight reconstruction--an approach which is forbidden in a proper analysis of obviousness.

application (see instant specification at p. 54, *ll.* 8-24; and U.S. Application No. 08/041,431, p. 17, *ll.* 12-27).[3]

The instant invention offers a major advantage over the yeast-based screening assays of the prior art. By providing a hybrid Gα protein that could adapt any receptor to the downstream yeast signaling pathway, the Applicants created a versatile universal host cell ready to accommodate any G-protein coupled receptor of interest for drug screening. Unlike the assay systems of Sledjiewski or King, the labor-intensive and cumbersome steps of constructing a hybrid receptor protein (Sledziewski) or identifying a mammalian receptor and Gα protein that could function in a yeast cell (King) with each new receptor to be assayed, were eliminated.

In view of the foregoing, the invention is not made obvious by the prior art.

CONCLUSIONS

Applicants respectfully request entry of the foregoing amendments and remarks into the file of the above-captioned patent application. For all the foregoing reasons, Applicants believe that the rejection of Claim 59 should be withdrawn and that Claim 59 is in condition for allowance.[4] All of the remaining rejections have been obviated by the cancellation of Claims 43-58 and 60. The declaration of an interference with the '188 Pausch patent is earnestly sought.

REQUEST FOR INTERFERENCE UNDER 37 C.F.R. § 1.607 WITH U.S. PATENT NO. 5,691,188 BY PAUSCH

Claim 59, which was constructively reduced to practice by the March 31, 1993 filing date of U.S. Application No. 08/041,431, is directed to the same or substantially the same subject matter as Claim 15 of the Pausch '188 patent. Since the application which matured to the Pausch '188 patent was filed on February 14, 1994, almost one year after the

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[3] We note that the Examiner has acknowledged that "there are no rejections under 35 U.S.C. § 112, first paragraph, applicable to the instant application" (Office Action dated June 20, 2003 at p. 4, first full paragraph).

[4] It is believed that the rejection of Claim 59 in view of Chang, which describes the FAR1 mutation involved in yeast cell cycle arrest, is not relevant to Claim 59, since Claim 59 does not have the limitation of a FAR1 mutation.

priority date of the instant application, Attorneys for Applicants allege under 37 C.F.R. § 1.608(a) that there is a basis upon which the Applicant is entitled to a judgment relative to the Pausch '188 patent.

An early allowance and declaration of an interference with the '188 Pausch patent is earnestly requested. The Examiner is invited to contact the undersigned to arrange an interview with the Attorneys for the Applicants to further discuss the foregoing.

Respectfully submitted,

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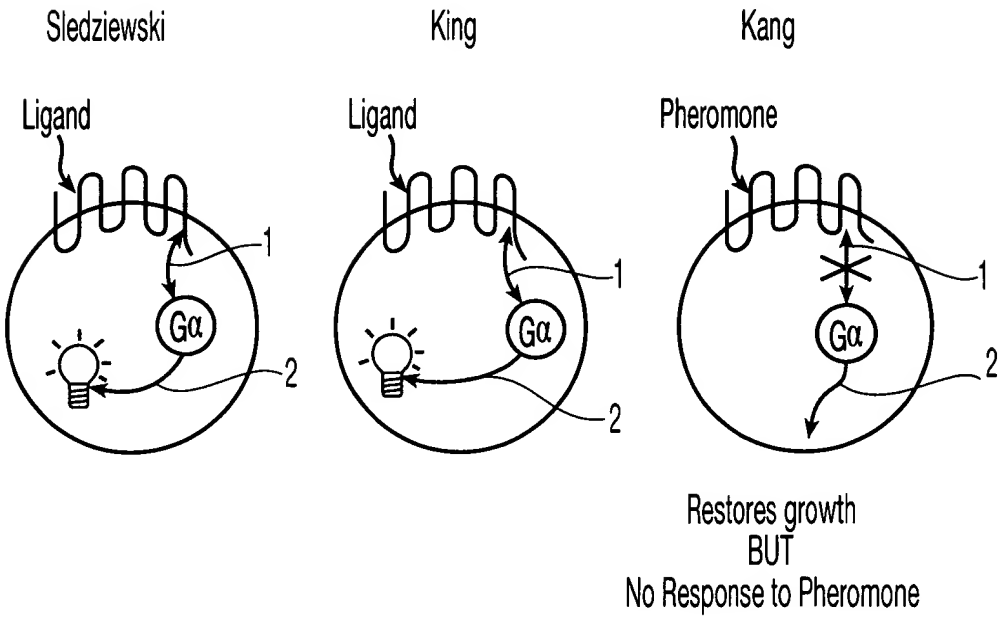
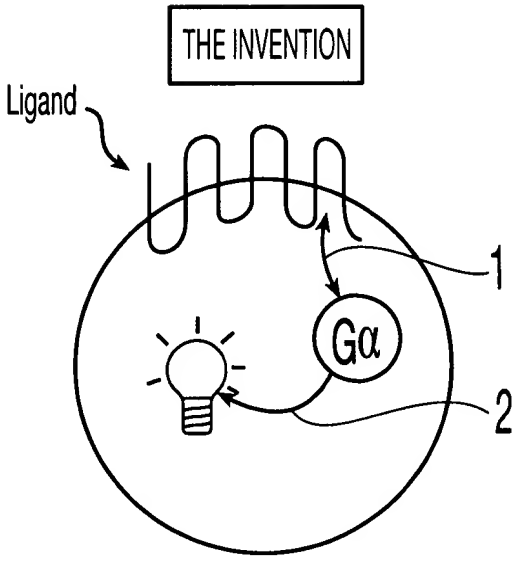
Enclosure

THE PRIOR ART



THE INVENTION



* yeast
* heterologous